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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FOLEY, SHANON A	
ART UNIT	**PAPER NUMBER**
1648	28

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/043,933	Applicant(s) BALLOUL ET AL.	
	Examiner Shanon Foley	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-20,25-31 and 79-120* is/are pending in the application.

4a) Of the above claim(s) *10-20,25-31,86,100 and 112* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *79-85, 87-99, 101-111, 113-120* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Request for Continued Examination

The request filed on 3/25/02 for a Request for Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/043933 is acceptable and a RCE has been established. An action on the RCE follows.

Claims 10-20, 25-31 and 79-120 are pending. Claims 10-20 and 25-31 are withdrawn from consideration due to a non-election of invention in paper no. 8. Claims 79-120 are under consideration. Applicant is reminded to cancel the claims 10-20 and 25-31 drawn to the non-elected invention.

Election/Restrictions

Newly submitted claims 86, 100 and 112 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The claims are drawn to the instantly claimed papillomavirus polypeptides being expressed from independent expression control elements. This limitation encompasses expression from an expression vector, which was the subject matter of group II in the restriction requirement of paper no. 7. Applicant elected group I with traverse in paper no. 8, drawn to a pharmaceutical composition comprising early and late proteins of the papillomavirus.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 86, 100, and 112 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 79-85, 87-99, 101-111, and 113-120 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 79-85, 87-99, 101-111, and 113-120 are indefinite because it cannot be determined what is included in the composition. The pharmaceutical composition "comprises" therapeutic agents, but "consists of" papillomavirus polypeptides (for example in claim 79) and an immunostimulatory polypeptide (for example in claim 91). Therefore, it is unclear what other therapeutic agents are "comprised" in the pharmaceutical formulations.

Claims 79, 91 and 108 are also unclear because an "intended" use of a composition is not evident from the ingredients. The intent of use would depend from the person in possession of the composition and not the composition itself. This rejection affects all dependent claims.

Claims 80, 83, 92, 95, 109 are vague and indefinite because the metes and bounds of what is intended by "nononcogenic variants" of E6 and/or E7 cannot be discerned. There is only one species of each described in the instant disclosure and other "variants" of each have not been described.

Claims 88, 104 and 116 are unclear because it cannot be determined how a carrier "allows" administration of a composition.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 80, 83, 92, 95, 109 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not teach the structural elements of the variants of E6 and/or E7. The specification reduces to practice only one species within the genus on page 18, line 34 and page 19, lines 4-8, the deletion-modified protein of E7, in which amino acids 21-26 have been deleted and the deletion-modified E6, in which amino acids 111-115 have been deleted. Since the genus embraces a wide variety of possible derivatives and variants of each polypeptide or protein, the single species of each polypeptide or protein is not seen as representative for the full genus claimed.

Claims 89, 105, 107, 117, and 118 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating or preventing cervical dysplasia or cancer caused by papillomavirus (HPV), does not reasonably provide enablement for treating or preventing all cervical cancer or dysplasia not caused by HPV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to treating or preventing cancer of the neck of the uterus by administering the instant compositions comprising papillomavirus polypeptides. The scope of the claims encompasses treating and preventing uterine cancer that is now caused by HPV.

Although HPV is attributed as a major cause for developing cervical neoplasia, there are other factors and or conditions under which the disease manifests, such as other sexually transmitted diseases and smoking. See the teachings of Dillner. (Journal of Clinical Virology. 2000; 19 (1-2): 7-23, abstract only). The working examples are limited to monitoring mortality and tumor growth after virus challenge, see example 6 on pages 26 and 27. There is no teaching provided in the specification that addresses other concerns in the art related to other causes of cervical carcinoma and there is no data that would convey to the skilled artisan that the instant formulations would be effective against other types of cervical cancers not caused by HPV. Therefore, due to the scope of the claims encompassing treating any form of cervical cancer not caused by HPV, the state of the art indicating other factors that are associated with the development of cervical cancer, the lack of guidance and the lack of working examples provided in the instant disclosure regarding these concerns in the art, it is determined that an undue amount of experimentation would be required by the skilled artisan to use the invention in its full scope.

Claims 108-120 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treat papillomavirus infections using the instant composition comprising the early proteins from the papillomavirus, does not reasonably provide enablement for prevent papillomavirus infections using the composition comprising the papillomavirus early proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a pharmaceutical composition to treat and prevent a papillomavirus infection or tumor consisting of early papillomavirus polypeptides E6 and E7 and a polypeptide having immunostimulatory activity. Galloway (Infectious Agents and Disease. 1994; 3 (4): 187-193) teaches that the early proteins from the papillomavirus are therapeutic in nature while the late proteins are prophylactic, see the abstract and the paragraph bridging pages 190 and 191. In example 6 of the instant disclosure on page 27, lines 5-24, tumor growth is retarded in mice by the administration of viruses expressing E6, E7, and IL-2. There is no data that would indicate that the mice were prevented from infection. Applicant also admits in the last paragraph of page 18 of the response that the early proteins, E5, E6, and E7 are therapeutic in nature. Therefore, due to the scope of the claims encompassing the prevention of papillomavirus infection with early proteins, which is a contrary to the teachings in the art, demonstrated by the teachings of Galloway, and the lack of data provided in the specification and working examples drawn to any preventative nature of these early polypeptides, it is determined that an undue amount of experimentation would be required of the skilled artisan to use the invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 79, 82, and 87-90 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Stanley et al. (US 6,096,869).

The claims are drawn to a pharmaceutical composition comprising as therapeutic agents early and late papillomavirus polypeptides consisting of E6, E7, L1, and L2 from HPV-16 that is injected to treat papillomavirus infection.

Stanley et al. teaches a pharmaceutical treatment composition comprising IL-12 and at least one papillomavirus protein, E1, E2, E4, E5, E6, E7, L1, and/or L2 of HPV-16 that is used to treat papillomavirus infections, lesions, and neoplasia that is injected. See column 3, lines 48-61 and column 5, lines 6-10.

Applicant submit since the new claims recite, "consisting of", the teachings of Stanley et al. do not anticipate the instant invention.

Applicant's arguments as well as a careful review of the newly submitted claims have been considered, but are found unpersuasive. As discussed above, it cannot be determined from the claim language what is intended to be encompassed by the pharmaceutical composition. Therefore, the additional component of IL-12 anticipates the instantly claimed formulations "comprising" additional ingredients. Moreover, since the treatment material of Stanley et al. incorporates "at least one of proteins E1, E2, E4, E5, E6, E7, L1, and/or L2", the composition of

Stanley et al. includes all of the proteins listed and any combination thereof, including E6, E7, L1, and L2. Therefore, the teachings of Stanley et al. anticipate claims 79, 82 and 87-90.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 91, 98, 99, 101-108, 110, and 115-120 rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley et al. supra, Galloway. (Infectious Agents and Disease. 1994; 3: 187-193), Hines et al. Obstetrics and Gynecology. 1995; 86 (5): 860-866), and Gajewski. The Journal of Immunology. 1996; 156: 465-472).

The claims are drawn to a pharmaceutical composition comprising HPV-16 polypeptides consisting of E6, E7, L1, and L2 in addition to an immunostimulatory molecule of IL-2 and B7.1.

The teachings of Stanley et al. are reiterated herein.

For applicant's convenience, the teachings of Galloway, Hines et al., and Gajewski cited in the Office action of 10/6/00 are copied below:

Galloway teaches a prospect for prophylactic vaccine to treat papillomavirus infections with a composition that includes L1and L2 proteins and therapeutic vaccines that include E6 and E7 proteins from the papillomavirus, see the abstract on page 187. Galloway also teaches that most individuals have antibodies that recognize the capsid proteins, especially L2, see the first paragraph of column 2 on page 189. In addition, rabbits immunized with L1 or L2 conferred protective immunity against the virus, see first full paragraph of column 2 on page 190. Galloway also teaches that L2 and E7 fusion proteins have reduced the number, severity, and duration of lesions. E7 was found to protect mice from a syngeneic tumor in an MHC-restricted fashion, see the paragraph bridging pages 190-191. Stimulation of the immune response against

E6 and/or E7 may be beneficial in clearing tumors, see the next to the last sentence of the second column on page 191. From the teachings of Galloway, one of skill in the art at the time of the invention would have been motivated to combine E6, E7, L1, and/or L2 into a vaccine to treat or prevent a papillomavirus infection. One of skill in the art at the time of the invention would have had a reasonable expectation of success because of the prophylactic properties of L1 and L2 to confer immunity and the treatment of tumors demonstrated by E6 and E7. Galloway does not teach the use of IL-2 and B7.1 to aid in activating the immune response.

Hines et al. teaches that the E7 oncoprotein peptide injected into mice induces a protective cell-mediated response against tumor formation after a challenge with HPV 16-transformed tumor cells in vivo. Immunization with peptides prevents tumor formation. Hines et al also proposes cell adoptive therapy treatment to accelerate tumor regression. This is accomplished by removing a patient's serum and stimulating their lymphocytes in vitro with a peptide, E6 and E7, and a cytokine, IL-2, and returned to the cancer patient as therapy, see the "cellular adoptive therapy" section on page 862-863 and figure 2 on page 863. Hines et al. concurs with Galloway in teaching that the major capsid proteins, L1, from the papillomavirus, see table 1 on page 861, mimicked the conformation of intact virions and were recognized by well-defined type-specific antibodies. Immunologically active virus-like particles used in a prophylactic vaccine would be successful because they are antigenic,, protective in animal models, and lack the viral DNA that would be carcinogenic in the host. Demonstrated again by the teachings of Hines et al., one of skill in the art at the time of the invention would have had a reasonable expectation of success because of the prophylactic properties of L1 and L2 to confer immunity and the treatment of tumors demonstrated by E6 and E7. Hines et al. does not teach the incorporation of B7.1 to aid in stimulating T cells.

Gajewski teaches that T cells require the participation of one additional "second signal" to secrete IL-2. This "second signal" capable of activating CD4+ and CD8+ T cells to secrete IL-2 is B7.1 and is used as a cofactor for IL-2 production and has been found to be necessary for the production of IL-2. B7.2 is also can also provide costimulator function for IL-2 production of CD4+ cells. Gajewski goes on to teach that the this aspect of cytotoxic T lymphocytes (CTL) would have a practical application in the development of tumor-specific immunotherapy, see the introduction on page 465. Expression of B7.1 human tumor cells can render them better able to stimulate alloreactive CD8+ lymphocytes to produce their own IL-2, see the first paragraph of the discussion section on page 470. The only difference between the claimed invention and the teachings of Gajewski is a direct papillomavirus vaccine that incorporates B7.1 and IL-2 along with the papillomavirus proteins E6, E7, L1 and/or L2.

One of skill in the art at the time the invention was made would have been motivated to combine the teachings of Galloway, Hines et al. and Gajewski to provide a prophylactic and a treatment vaccine that would represent the major antigens of the papillomavirus and with an enhanced ability to stimulate T cells with IL-2 and B7.1. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because of the success taught by Galloway and Hines et al. in preventing papillomavirus infections with a composition that includes L1and L2 and therapeutic vaccines that include E6 and E7 proteins from the papillomavirus. The addition of IL-2 to a vaccine composition taught by Hines et al. would be advantageous in stimulating T cell response. The importance of stimulating IL-2 was taught by Gajewski as well as the capability

of B7.1 to stimulate a T cell response to produce IL-2. Therefore, it would have been prima facie obvious to one skilled in the art at the time the invention was made to combine the teachings of the references to make a successful vaccine for the treatment and prevention of papillomavirus infections.

On page 18 of the response, it is appreciated that applicant admits that "the person skilled in the art would have used L1 or L2 capsid protein to provide protection against HPV infection or E5, E6 or E7 polypeptides to retard the development of HPV-infected tumors as taught by Galloway, or L1 and L2 capsid proteins as taught by Hines et al."

Applicant argues, however, that there is no suggestion to combine the four specified proteins. Applicant also reminds the Office of the discussion in previous arguments by applicant that the L2 and E7 combination were found ineffective. Applicant further argues that Hines et al. teaches away from the claimed invention because the reference seems to stress in vitro stimulation of lymphocytes is more effective than in vivo stimulation by the host. On this basis, Applicant concludes that the ordinary artisan would not have been motivated to administer E6 and E7 with an immunostimulatory molecule. In addition, applicant asserts that the presence of IL-2 in cultured lymphocytes is to induce cytotoxic activity and is not used as a therapeutic agent.

Applicant's arguments and a review of the references cited have been considered, but are found to be unpersuasive. The suggestion to combine the four specified peptides is not only suggested, but is anticipated by the teachings of Stanley et al., see the discussion above. Further, as applicant has admitted, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the early therapeutic proteins, E6 and E7 with the prophylactic late proteins, L1 and L2, of Galloway to treat and prevent infection, regardless of

whether the patient was already infected or not. Applicant's arguments with respect to the ineffectiveness of the E7 + L2 combination is moot since there is no basis for exclusion in the claims instantly pending and there is no basis for support for the specific exclusion in the instant disclosure.

In response to arguments directed against the teachings of Hines et al., it is determined that the teachings of the reference are broader than applicant's interpretation. In the phrase recited by applicant, Hines et al. is discussing the immune response to direct administration of viral antigens only and not the additional administration of a cytokine. Hines et al. teaches that the extracted lymphocytes are stimulated with the peptides and the cytokines (emphasis added), which activates the cytotoxic T lymphocytes, see the same section recited by applicant and figure 2 on page 863. Therefore, the teachings of Hines et al. establishes that cytokines, i.e., IL-2, activates cytotoxic T cells. The teachings of Stanley et al. further establish the critical factor of administering a cytokine for treating papillomavirus infections, see column 2, line 48 to column 8, line 42 and the claims. Therefore, one of ordinary skill in the art would have been motivated to administer a cytokine, i.e. IL-2, with the HPV polypeptides of Stanley et al. or Galloway to directly stimulate a patient's cytotoxic T cells and eliminate the possibility of contamination by re-introducing cells stimulated in vitro in the method of Hines et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because Stanley et al. teaches the importance of administering a cytokine to stimulate T cells to reduce HPV-induced tumors see column 1, line 65 to column 2, line 35 and Hines et al. teaches that the cytokine IL-2 is a natural stimulator of cytotoxic T cells.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention as made, absent unexpected results.

Claims 80, 81, 83-85, 92-97, 109, 113, and 114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley et al., Galloway, Hines et al., and Gajewski as applied to claims 79, 82, 87-91, 91, 98, 99, 101-108, 110, and 115 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105).

The claims are drawn to nononcogenic variants of E6 having amino acids 111-115 deleted and E7 having amino acids 21-26 deleted.

None of the before-mentioned references teach the specific nononcogenic fragments of E6 or E7.

However, Crook et al. teaches that an amino acid deletion of residues 111-115 in E6 reduces binding to p53. Munger et al. teaches that the amino acid residues in HPV-16 E7 necessary to form a complex with retinoblastoma tumor suppressor gene is located surrounding the cysteine residue at position 24.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the specific deletions taught by Munger et al. and Crook et al. to significantly decrease or eliminate tumor suppressive effects of these proteins. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because Stanley et al. teaches that the HPV proteins in the pharmaceutical formulation are also antigenic fragments, see the previous citations and the proteins comprising the specific residue deletions taught by Crook et al. and Munger et al. would be antigenic fragments. Therefore, the invention as a whole would have been prima facie

obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SAF
Shanon Foley/SAF
June 1, 2002

James C. Housel
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